CLINICAL TRIAL SUMMARY REPORT

EUDRACT NUMBER: 2009-017099-25

14 December 2011

A Pilot Pharmacodynamic/Pharmacokinetic Study of Fluticasone Propionate Administered as a Dry Powder in Patients with Asthma

Protocol No:	OTT329/301
Development Phase:	Phase I/IIa
Investigational Product:	Flovent® Diskus® 50 (fluticasone propionate 50 µg)
Indication:	Asthma
Date of Admission of First Subject:	19 November 2009
Date of Follow-up of Last Subject:	18 October 2010
Date of Final Report:	22 September 2011
Sponsor Representative:	[redacted] PhD
Sponsor:	Oriel Therapeutics, Inc Post Office Box 14087 Research Triangle Park, NC 27709 United States of America
Principal Investigator:	Darren Wilbraham MBBS, DCPSA
Investigating Site:	Quintiles Drug Research Unit at Guy's Hospital 6 Newcomen Street, London SE1 1YR United Kingdom Tel: 0207 910 7700 Fax: 0207 910 7800

This Clinical Trial was conducted, and essential study documentation archived, in compliance with International Conference on Harmonization Guidelines and Good Clinical Practice (ICH-GCP)

<table>
<tr><td colspan="2">Name of Sponsor/Company:
Oriel Therapeutics, Inc., a Sandoz Company

Name of Finished Product:
Flovent® Diskus® 50
Name of Active Ingredient:
Fluticasone propionate</td><td>Individual Study Table Referring to Part of the Dossier:

Volume:

Page:</td><td>(For National Authority Use Only)</td></tr>
<tr><td colspan="4">Title of Study:
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<tr><td colspan="4">Investigator:
Darren Wilbraham MBBS, DCPSA</td></tr>
<tr><td colspan="4">Study Center:
Quintiles Drug Research Unit at Guy's Hospital, 6 Newcomen Street, London SE1 1YR, United Kingdom</td></tr>
<tr><td colspan="4">Publication (reference):
Not applicable</td></tr>
<tr><td colspan="2">Study Period (years):
(Date of first enrollment)
(Date of last completed)</td><td>19 November 2009
18 October 2010</td><td>Phase of Development:
I/IIa</td></tr>
<tr><td colspan="4">Objectives:
Primary Objective:
To investigate the pharmacodynamics (PD) of increasing doses of fluticasone administered as a dry powder in asthma patients with the intent to better characterize the early time course of changes in the inflammatory PD marker Fractional Expired Nitric Oxide (FENO).
Secondary Objective:
To investigate the pharmacokinetics (PK) and safety of fluticasone administered as a dry powder.</td></tr>
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Methodology:

This was a single-center, multiple-dose, randomized, 3-period crossover study in patients with asthma. The study investigated the PD, PK and safety of multiple dose administration of increasing doses of fluticasone administered by dry powder oral inhalation using Flovent® Diskus®50. One dosage strength (50 µg/puff) of fluticasone was to be administered via Diskus® with 1, 2 or 4 puffs for 5 days (BID for Days 1 to 4 with a single dose on Day 5). After interim analysis, treatments were amended to 1, 2 or 4 puffs for 5 days QD. The study was structured as a randomized 3-period cross-over design. Each subject received each of the 3 treatments in a sequence designed to provide overall balance over the 3 periods.

Within each treatment period, pre-treatment measurements of FENO and lung function were made and these were monitored throughout the treatment period. On Days 1 and 5 blood samples were also drawn at prescribed time points for analysis of fluticasone levels. The subjects were discharged following the final blood draw and FENO measurement on Day 5. Plasma concentrations of fluticasone were measured and evaluated in a pharmacokinetic analysis of samples taken after the first and the last dose.

There was a washout period (from last dose administration of preceding period to first dose administration of the following period) of approximately 7 to 14 days between treatments.

The end of the study was the last assigned follow-up visit, 5 to 7 days after the last dose was administered.

Number of subjects (planned and analyzed):

Twenty four (24) subjects were planned and 24 subjects (14 male and 10 female) were enrolled

Diagnosis and main criteria for inclusion:

Diagnosis:

Patients with mild to moderate asthma (Global Initiative in Asthma [GINA]).

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Criteria for inclusion:

1. Adult males and females ≥18 years with body mass index (BMI) 19 to 30 kg/m^2 (inclusive) and a body weight ≥50 kg.
2. Subjects with a clinical diagnosis of mild to moderate asthma (defined as satisfying the GINA definition of asthma or had satisfied in the past and have a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥50% at screening.
3. Subjects with FENO levels at screening and Day 1 pre-dose of ≥50 ppb.
4. Subjects who if female, were not currently pregnant or breast feeding and were using medically acceptable methods of contraception.
5. Subjects receiving inhaled, oral or parenteral corticosteroid treatment within 4 weeks of randomization or who had been intubated for ventilation in the past 5 years or were considered to have very severe asthma were excluded from the study.
6. Subjects whose clinical laboratory test results were not clinically relevant and were acceptable to the Investigator.
7. Subjects who were negative for hepatitis B surface antigen (HBsAg), hepatitis C antibody and human immunodeficiency virus (HIV) I and II test at screening.
8. Subjects who were negative for drugs of abuse and alcohol tests at screening and admission.
9. Subjects who were non-smokers for at least 3 months prior to screening.
10. Subjects who had a <10 pack-year smoking history.
11. Subjects who were able and willing to give written informed consent.
12. Subjects who were able to use an inhaled medical device, as demonstrated by the use of a flow loop assessment.
13. Medical history was to be verified by either a personal physician or medical practitioner as appropriate.

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Criteria for exclusion:

1. Subjects who did not conform to the above inclusion criteria.
2. Subjects who had a clinically relevant history or presence gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, connective tissue diseases or disorders which would have precluded participation in the opinion of the Investigator.
3. Subjects who had a clinically relevant medical or surgical history that would have precluded the administration of inhaled corticosteroids as indicated in the patient information leaflet for Flixotide Accuhaler or Flovent Diskus.
4. Subjects who had a history of relevant drug hypersensitivity.
5. Subjects who had a history of alcoholism.
6. Subjects who had a history of drug abuse.
7. Subjects who had received steroid treatment in the prior month or were taking concomitant medications likely to interfere with FENO production.
8. Subjects who were currently taking inhibitors of CYP3A4 such as ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, or telethromycin.
9. Subjects who consumed more than 28 units (male)/ 21 units (female) of alcohol a week. 1 unit = 1 (125 mL) glass of wine = 1 measure of spirits = ½ pint of beer.
10. Subjects who had a significant infection or known inflammatory process on screening.
11. Subjects who had acute gastrointestinal symptoms at the time of screening and/or admission (e.g. nausea, vomiting, diarrhoea, heartburn).
12. Subjects who had an acute respiratory infection such as influenza at the time of screening and/or admission.
13. Female subjects who were pregnant, trying to become pregnant, breast feeding, or not using an acceptable method of contraception.

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Criteria for exclusion (continued):

14. Subjects who had used any investigational drug in any clinical trial within 3 months of receiving the last dose.
15. Subjects who had received the last dose of investigational medicinal product (IMP) greater than 3 months ago but who were on extended follow-up requiring blood sampling.
16. Subjects who had anemia at screening.
17. Subjects who were using medication, which in the opinion of the Investigator would have affected the outcome of the study.
18. Subjects who had donated and/or received any blood or blood products within the previous 3 months prior to first dosing (to review on a case by case basis).
19. Subjects who could not communicate reliably with the Investigator.
20. Subjects who were unlikely to co-operate with the requirements of the study.

Test product, dose and mode of administration, batch number:

Fluticasone was administered as a dry powder by oral inhalation via Flovent® Diskus® 50 (50 µg/puff fluticasone). The study drug lot numbers were R425022 and R425019.

Daily doses administered were as follows:

- 1 puff (50 µg) BID/QD fluticasone
- 2 puffs (100 µg) BID/QD fluticasone
- 4 puffs (200 µg) BID/QD fluticasone

Reference product, dose and mode of administration, batch number:

Not applicable.

Duration of treatment:

Treatment was administered for 5 days as one of the following:

- BID dosing on Days 1 to 4 and a single dose on Day 5 for Subjects [redacted] to [redacted].
- QD dosing on Days 1 to 5 for Subjects [redacted] to [redacted].

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Bioanalytical method:
Plasma samples were analyzed for fluticasone concentration at Tandem Labs (Salt Lake City, UT, USA) using an LC/MS/MS method with a quantitative range from 1.00 to 200 pg/mL.

Criteria for evaluation
Pharmacokinetics:
The following pharmacokinetic parameters for fluticasone were calculated:

- AUC_{τ} (pg*h/mL) – Area under the plasma concentration-time curve to the last quantifiable concentration within the dosing interval, calculated using the linear trapezoidal rule
- C_{max} (pg/mL) – Peak observed plasma concentration over the dosing interval directly obtained from the plasma concentration time data, without interpolation
- T_{max} (h) – Time to peak plasma concentration directly obtained from the plasma concentration time data, without interpolation.

Pharmacodynamics:
FENO was measured pre-dose and every 1 to 4 hours post-dose on Days 1 to 5 while the subjects were in the clinic. Due to the exploratory nature of this study, several interpretations of ICS effects on FENO were to be analyzed. Area under the FENO concentration-time curve (expressed as % change from baseline, AUC-FENO) was the primary outcome that was derived from the dataset. In addition, maximum % and absolute change in FENO from baseline (Delta max FENO, Delta max % FENO) and time to inhibition to normal range [≤20 ppb FENO (tnormal)] were determined. Lung function tests (FEV_1, FVC and PEF) were also performed each morning prior to the morning dose and percent change from baseline was calculated.

Safety:
The safety evaluation included the measurement of vital signs (blood pressure, pulse rate and body temperature), clinical laboratory tests (hematology, serum biochemistry, and urinalysis; urine microscopy, if required) and the monitoring and recording of AEs.

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Statistical methods

Pharmacokinetic parameters:

Individual subject plasma fluticasone propionate concentrations and actual sampling times were listed by treatment and protocol sampling time and summarized using descriptive statistics — N, arithmetic mean, standard deviation, and coefficient of variation, geometric mean and coefficient of variation, and minimum, median, and maximum. Individual subject PK parameters were listed by treatment and summarized using descriptive statistics — N, arithmetic mean, standard deviation, and coefficient of variation, geometric mean and coefficient of variation, and minimum, median, and maximum. Individual subject and arithmetic mean plasma fluticasone propionate concentrations were displayed graphically by treatment.

PK parameters — C_{max} and $AUC_{(0\text{-}12)}$ — were compared among treatments using the power model, i.e. $P = a \times Dose^{b}$ where P represents the parameter and a and b are constants. A log-log plot of P versus Dose will be linear and a value of a of ≈ 1 indicates linear pharmacokinetics.

Pharmacodynamic parameters:

Individual subject absolute and percent change from baseline FENO and actual sampling times were listed by treatment and protocol sampling time. Absolute and percent change from baseline FENO were summarized using descriptive statistics — N, arithmetic mean, standard deviation, and coefficient of variation, geometric mean and coefficient of variation, and minimum, median, and maximum. Individual subject PD parameters were listed by treatment and summarized using descriptive statistics — N, arithmetic mean, standard deviation, and coefficient of variation, geometric mean and coefficient of variation, and minimum, median, and maximum. Individual subject and arithmetic mean values for absolute and percent change from baseline FENO were displayed graphically by treatment.

Safety parameters:

All safety assessments, including AEs, clinical laboratory evaluations, vital signs, 12-lead ECG results, physical examinations were listed and where appropriate summarized with descriptive statistics.

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Results

Pharmacokinetic results:

There was a dose-related and reasonably dose proportional increase in the mean and individual subject plasma concentrations, C_{max}, and $AUC_{(0-t)}$ of fluticasone propionate on Day 1 and Day 5 after administration of 50 µg, 100 µg, and 200 µg BID or QD for 4.5 days. There was graphical evidence, however, of increases in systemic exposure that were slightly lower than dose-proportionality would predict.

Pharmacodynamic results:

There was no evidence of dose separation in the BID regimen with respect to the FENO pharmacodynamic response. The QD regimen showed a dose-related decrease in FENO on average in the patient population, although not every individual displayed a dose dependent effect on FENO.

There was essentially no separation among doses and regimens with respect to the mean and individual subject pulmonary function tests — absolute and percent predicted FEV_1, FVC, and PEF.

There was a reasonably linear relationship between the area under the effect curve $[AUEC_{(0-108)}]$ for FENO absolute and percent change from baseline and fluticasone propionate C_{max} and $AUC_{(0-t)}$ on Day 5, suggesting a decrease in FENO, i.e. less inflammation, as exposure to fluticasone propionate increases.

Safety results:

Fluticasone, administered as 1, 2 or 4 puffs BID/QD for 5 days via the Flovent® Diskus® 50 was well tolerated by the mild to moderate asthmatics on this study.

A total of total 27 TEAEs were reported by 16 (67%) of the 24 subjects. The most frequently reported TEAEs were headache (6 events), chest discomfort (3 events), abdominal pain (2 events) and rhinorrhoea (2 events). With the exception of one moderate TEAE of asthma, all TEAEs were mild. There were no deaths or SAEs.

There were no clinically relevant trends in clinical laboratory data, vital signs data or physical examination findings between the different treatments or over time.

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Conclusions:

- Once daily treatment with fluticasone may provide a viable dynamic, dose-responsive PD model of bronchial inflammation, as measured by FENO production.
- There was a separation of fluticasone doses in mean FENO (absolute and percent change from baseline) response when QD dosing was employed, although not all individuals demonstrated a clear dose response.
- There was no separation among doses for the BID regimen and regimens with respect to the mean and individual subject FENO absolute and percent change from baseline.
- It appears that only half the asthma population, as defined by the current inclusion criteria, will be dose sensitive to fluticasone in the 50 to 200 µg range; approximately half of patients are expected to have a maximal FENO response to 50 µg fluticasone.
- There was a reasonably linear relationship between the $AUEC_{(0\text{-}108)}$ for FENO absolute and percent change from baseline and fluticasone propionate C_{max} and $AUC_{(0\text{-}t)}$ on Day 5, suggesting a decrease in FENO, i.e. less inflammation, as exposure to fluticasone propionate increases.
- There was essentially no separation among doses and regimens with respect to the mean and individual subject pulmonary function tests — absolute and percent predicted FEV_1, FVC, and PEF.
- There was a dose-related and reasonably dose-proportional increase in the mean and individual subject plasma concentrations, C_{max}, and $AUC_{(0\text{-}t)}$ of fluticasone propionate on Day 1 and Day 5 after administration of 50 µg, 100 µg, and 200 µg BID or QD for 4.5 days. There was graphical evidence, however, of increases in systemic exposure that were lower than dose-proportionality would predict.
- Fluticasone, administered as 1, 2 or 4 puffs BID/QD for 5 days via the Flovent® Diskus® 50 was well tolerated by the mild to moderate asthmatics on this study.